2024

# ADC CONSENSUS SYMPOSIUM

主編 台灣乳房醫學會






台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

# Preface

目前，乳癌在台灣女性癌症中，發生率仍位居第一名。近年來，隨著抗體藥物複合體（ADC）技術的迅速發展，我們逐漸看見它在乳癌治療中的潛力和改變未來治療策略的能力。然而，隨著治療選項日益多元，如何為每一位病友選擇最適合的治療方式，也成為臨床醫師所面臨的挑戰，因此，需要更全面的指引來協助制定最佳治療計畫。

為了整合關於 ADC 在晚期乳癌治療中的最新知識和臨床應用，台灣乳房醫學會於 2024 年 8 月邀請多位專家成立共識會議籌備工作小組，針對 HER2 陽性、HR 陽性 /HER2 陰性以及 HR 陰性 /HER2 陰性乳癌的治療策略，進行系統性的研究回顧與討論，並涵蓋與生物標記、毒性管理及未來治療方向相關的議題。經過多次籌備會議，於 2024 年 12 月 29 日成功舉辦「2024 ADC Consensus Symposium」，凝聚專家學者的共識並彙整成果，經台灣乳房醫學會第九屆理監事審議通過，完成了本次共識會議手冊。

本手冊的制定，旨在為臨床醫師提供更明確的指引，以支持 ADC 藥物在乳癌治療中的最佳應用，從而提升病患的生存率及生活品質。同時，我們希望這份共識能促進醫療專業人員間的合作與知識交流，為台灣乳癌治療作出更多貢獻。

在此，我謹代表台灣乳房醫學會，衷心感謝所有參與本次共識會議的專家學者。特別感謝以下專家對本次會議的寶貴貢獻（依姓氏筆畫排列、職稱省略概以醫師稱謂）：

于承平、王明暘、李國鼎、沈士哲、沈陳石銘、周旭桓、林季宏、林金瑤、侯明鋒、俞志誠、洪志強、洪進昇、張金堅、張振祥、張源清、張獻崑、張端瑩、張耀仁、莊捷翰、許志怡、郭文宏、郭玟伶、陳守棟、陳怡君、陳芳銘、陳訓徹、陳達人、彭夢婷、曾令民、馮安捷、黃至豪、黃其晟、黃俊升、黃柏翔、楊明翰、葉顯堂、廖國秀、趙大中、趙祖怡、劉良智、劉峻宇、蔡宜芳、鄭翠芬、盧彥伸、賴峻毅、戴明燊、鍾為邦、饒坤銘等諸位醫師。

本治療共識僅做為參考，因每人狀況不同，而由各醫師選擇最適當之處置方式，不作為醫療訴訟用。

最後，感謝所有醫療專業人士的投入和支持，期望本手冊的發布與應用，能為乳癌治療帶來更多的價值與成果。

台灣乳房醫學會 理事長

陳守棟 于 2025 年 2 月

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# Contents





# Strength of the Recommendation and Quality of Evidence

| Strength | Recommendation |
|---|---|
| A | Strong recommendation for use |
| B | Moderate recommendation for use |
| C | Marginal recommendation for use |
| D | Recommendation against use |

| Quality | Evidence |
|---|---|
| I | Evidence from at least 1 properly designed randomized, controlled trial |
| II | Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results of uncontrolled experiments |
| III | Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies |


1. AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2012; 182: E839–E842
2. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011; 66:8
3. Annals of Hematology (2018) 97:1271–1282


# The Principle of Voting for Strength of Recommendation

| Strength | Recommendation |
|---|---|
| A | Strong recommendation for use |
| B | Moderate recommendation for use |
| C | Marginal recommendation for use |
| D | Recommendation against use |

For the “Strength of Recommendation A and B”, a majority panel vote of at least 85% is required.

For the “Strength of Recommendation C”, a panel vote of at least 50% (but less than 85%) is required.

For recommendations where there is strong panel disagreement regardless of the quality of the evidence, “Strength of Recommendation D” requires a panel vote of at least 25%.


1. NCCN giudelines. Development and Update of Guidelines.


2024 ADC CONSENSUS SYMPOSIUM

# Is ADC simply an upgraded targeted chemotherapy or an innovative agent?

—— 高醫附醫 / 高理鈞 醫師

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Antibody–drug conjugates (ADCs) are biopharmaceuticals that combine a highly potent cytotoxic payload conjugated to a target–specific monoclonal antibody via a linker, improving the therapeutic window and reducing off–target effects. | I | A | 1–4 |
| 2. The anti–tumor efficacy of ADCs can be attributed to the following mechanisms:<br>① Upon binding to the antigen on cancer cells, the ADC is internalized and releases its cytotoxic payload.<br>② The released payload may induce a bystander effect, thereby enhancing the efficacy of ADCs.<br>③ In addition, the anticancer activity of ADC may also engage in antibody–dependent cell–mediated cytotoxicity (ADCC), antibody–dependent cellular phagocytosis (ADCP), and complement–dependent cytotoxicity (CDC) effects. | ① II<br>② II<br>③ III | ① A<br>② A<br>③ C | 5–8 |
| 3. The innovative mechanisms of ADCs set them apart from conventional targeted chemotherapies. Nevertheless, each ADC exhibits unique properties. | I | A | 9 |

## ◎ Reference


1. Makawita S, Meric-Bernstam F. Antibody-drug conjugates: patient and treatment selection. *Am Soc Clin Oncol EducBook* 2020;40:105—14.
2. Leung D, Wurst JM, Liu T, et al. Antibody conjugates-recent advances and future innovations. *Antibodies (Basel)* 2020;9(1):2.
3. Adair JR, Howard PW, Hartley JA, et al. Antibody–drug conjugates – a perfect synergy. *Expert Opin Biol Ther* 2012;12(9):1191–206.
4. Lambert JM, Berkenblit A. Antibody–Drug Conjugates for Cancer Treatment. *Annu Rev Med* 2018;69:191–207.
5. Birrer MJ, Moore KN, Betella I, et al. Antibody–Drug Conjugate–Based Therapeutics: State of the Science. *J Natl Cancer Inst* 2019;111(6):538–49
6. Staudacher AH, Brown M. Antibody drug conjugates and bystander killing: is antigen–dependent internalisation required? *Br J Cancer* 2017;117:1736–42
7. Tai YT, Mayes PA, Acharya C et al. Novel anti—B–cell maturation antigen antibody–drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. *Blood* 2014;123:3128—3138.
8. Radocha J, van de Donk NWCJ, Weisel K. Monoclonal Antibodies and Antibody Drug Conjugates in Multiple Myeloma. *Cancers (Basel)* 2021;13(7):1571.
9. Fu Z, Li S, Han S, et al. Antibody drug conjugate: the “biological missile” for targeted cancer therapy. *Sig Transduct Target Ther 2022;7:93*.

# Definition, detection, and reproducibility of the HER2-ultralow category

—— 臺北榮總 / 許志怡 主任

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. HER2–ultralow is defined as HER2 IHC 0 with membrane staining (faint, partial membrane staining in ≤ 10% of tumor cells). | I | A | 1 |
| 2. Due to notable inter–assay variabilities in the HER2 IHC test, one may consider using the 4B5 kit with its validated staining protocol as a companion test.* | II | B | 1–3 |
| 3. Before assigning a score of HER2 IHC 0 (no staining), pathologists examine the entire tumor area under high–power magnification (40x objective) to confirm the absence of any faint partial membrane staining.† | II | B | 4 |

* The suggested 4B5 kit with standard protocol was employed in the DESTINY Breast–06 trial; nevertheless, other validated assays may be acceptable for assessing HER2 status.

† Non–specific basal staining resulting from the retraction artifact should be disregarded. Only linear intercellular membrane staining is considered acceptable.

## ◎ Reference


1. Bardia A, Hu X, Dent R, et al. Trastuzumab Deruxtecan after Endocrine Therapy in Metastatic Breast Cancer. N Engl J Med. 2024;391(22):2110–2122.
2. Hempenius MA, Eenkhoorn MA, Høeg H, et al. Quantitative comparison of immunohistochemical HER2–low detection in an interlaboratory study. *Histopathology*. 2024;85(6):920–928.
3. Salgado RF, Bardia A, Curigliano G, et al. Human epidermal growth factor receptor 2 (HER2)–low and HER2–ultralow status determination in tumors of patients (pts) with hormone receptor—positive (HR+) metastatic breast cancer (mBC) in DESTINY–Breast06 (DB–06). *Ann Onc*ol. 2024; 35:S1213 – S1214.
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6. Kim MC, Kwon SY, Jung HR, Bae YK. Impact of immunohistochemistry staining conditions on the incidence of human epidermal growth factor receptor 2 (HER2)–low breast cancer. *Virchows Arch*. 2024;485(6):1117–1125.

# Integrating ADC into the treatment roadmap of HER2-positive advanced breast cancer

—— 臺大醫院 / 王明暘 醫師 & 臺大醫院 / 楊明翰 醫師

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Trastuzumab deruxtecan (T–DXd) is indicated in patients with HER2–positive metastatic breast cancer previously treated with a taxane and trastuzumab with/without pertuzumab in the metastatic setting. T–DXd is the preferred second–line option yet still demonstrates activity after Trastuzumab emtansine (T–DM1) as a third– or later–line option. | I | A | 1–4 |
| 2. T–DM1 is indicated in patients with HER2–positive advanced breast cancer, who had been previously treated with a taxane and trastuzumab with/without pertuzumab in the metastatic setting. T–DM1 is a second– or later–line treatment option after progression on a taxane and trastuzumab with/without pertuzumab in cases where/when T–DXd is not available. | I | A | 5–7 |
| 3. If T–DXd is discontinued due to toxicity, such as interstitial pneumonitis, T–DM1 can be considered as a subsequent treatment option. | II | A | 1, 2, 4 |
| 4. T–DXd demonstrates central nervous system (CNS) activity in patients with HER2–positive advanced breast cancer. This includes efficacy in those with active brain metastases, both newly diagnosed and previously–treated brain metastases that are progressing. | I | A | 8, 9 |
| 5. T–DM1 shows potential as a treatment for HER2–positive breast cancer in patients with brain metastases, particularly when the metastases are stable and in cases where/when T–DXd is not available. | II* | B | 10 |

* Based on an exploratory analysis of a phase IIIb trial (KAMILLA) and some published real world data.

## ◎ Reference


1. Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. *N Engl J Med*. 2022;386(12):1143–1154.
2. Cortés J, Hurvitz SA, Im SA, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in HER2–positive metastatic breast cancer: long–term survival analysis of the DESTINY–Breast03 trial. *Nat Med*. 2024;30(8):2208–2215.
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6. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2–positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open–label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732–742.
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# Integrating ADC into the treatment roadmap of HR-positive/HER2-negative advanced breast cancer

——北醫附醫 / 洪進昇 主任

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Fam–T–DXd can be used in patients who have progressed upon endocrine therapy and ≥ 1 line of chemotherapy in HR–positive/HER2 IHC 1+ or 2+/ISH negative metastatic breast cancer (MBC). | I | A | 1 |
| 2. T–DXd is an effective treatment option for patients with HR–positive/HER2–low or ultralow MBC after ≥ 1 prior line of endocrine therapy (ET). | I | A | 2 |
| 3. Anti–TROP2 ADC (ex. Sacituzumab govitecan (SG)) may be used for HR–positive/HER2–negative metastatic or locally advanced unresectable breast cancer after prior treatment including ET, a CDK4/6 inhibitor, and ≥ 2 lines of chemotherapy in the MBC. | I | A | 3, 4 |
| 4. Subgroup analysis demonstrated anti–TROP2 ADC (ex. SG) used in HR–positive/HER2–negative MBC, including HER2–low and HER2 IHC0, are consistent with overall population. | II* | A | 3, 4 |
| 5. Both ADCs (T–DXd and SG) proved activity in patients with metastatic HER2–low, HR–positive BC after refractory to ET. Currently, if patients received chemotherapy, T–DXd is more preferred after ≥ 1 line of chemotherapy, but no appropriate direct comparison is available now between T–Dxd and SG after ≥ 2 lines of chemotherapy. | II | B | 5 |
| 6. There is currently insufficient evidence to support using an ADC after progression on prior ADC in HR–positive/HER2–negative (include HER2–low, –ultralow and IHC0) MBC. | II | B | 6, 7 |
| 7. Dato–DXd is potential new option for patients with previously treated, endocrine–resistant HR–positive/HER2–negative mBC. It was associated with improved progression–free survival (PFS), regardless of prior duration of CDK4/6 inhibitors and presence/absence of brain metastases at baseline. (FDA Not approved until Dec. 29, 2024) | I | A | 8 |

* Although this statement is from a randomized trial, the subgroup analysis is not the primary endpoint and the quality of evidence is questionable.

## ◎ Reference


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# Integrating ADC into the treatment roadmap of HR-negative/HER2-negative advanced breast cancer

——三軍總醫院 / 廖國秀 主任

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. In HR–negative/HER2–negative advanced breast cancer, current evidence support the use of SG for patients who have progressed after receiving ≥ 2 prior therapies (with at least 1 line in the metastatic setting). | I | A | 1 |
| 2. In HR–negative/HER2–low advanced breast cancer, current evidence support the use the T–DXd for patients who have progressed upon ≥ 1 lines of chemotherapy in the metastatic setting. | I | A | 2 |
| 3. There is no sufficient evidence support using an ADC after progression on prior ADC in HR–negative/HER2–low MBC. | II | B | 3, 4 |
| 4. Both ADCs (T–DXd and SG) proved activity in patients with metastatic HER2–low triple–negative breast cancer (TNBC). | II | B | 1, 2 |
| 5. SG could be considered before T–DXd in this setting. | II | B | 1–4 |

## ◎ Reference


1. ESMO Open, Volume 8, Issue 1, May 2023.
2. Bardia A, Rugo HS, Tolaney SM, et al. Final Results From the Randomized Phase III ASCENT Clinical Trial in Metastatic Triple–Negative Breast Cancer and Association of Outcomes by Human Epidermal Growth Factor Receptor 2 and Trophoblast Cell Surface Antigen 2 Expression. J Clin Oncol. 2024;42(15):1738–1744.
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4. NCCN breast. 2024 v6.

# Biomarker issues for ADC

—— 成大醫院 / 李國鼎 主任

## Biomarker issues for ADC ：HER2

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Expression of HER2 is the only biomarker to predict the therapeutic efficacy of T-DM1 and T-DXd in breast cancer patients.* | I | A | 1-4, 8 |

* ・HER2 expression (HER2-positive) could predict the therapeutic efficacy of T-DM1.
・Comparing with chemotherapy, HER2-low expression could predict better progression free and overall survival (OS) in MBC patients treated with T-DXd.
・In DESTINY Breast-06 trial, HR-positive/HER2-low/-ultralow expression could predict better PFS than chemotherapy in the MBC patients treated with >= 1 lines of ET.
・HER2-null (completely unstained for HER2 by IHC)
HER2-ultralow (IHC 0 with membrane staining, defined as 0< IHC <1+)
HER2-low (IHC 1+ or IHC 2+/ISH negative)
HER2-positive (IHC 3+, 2+/ISH positive)

## Biomarker issues for ADC — TROP2

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Based on current evidence, examination of TROP-2 expression level is not necessary if SG therapy is considered.† | I | A | 5-7 |

† ・In TroPiCS-02 trial for HR-positive/HER2-negative MBC, SG has better OS over treatment of physician's choice (TPC) regardless of TROP-2 expression levels.
・In ASCENT trial for metastatic TNBC, SG improved clinical outcomes over TPC regardless of TROP-2 expression levels.

## ◎ Reference


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2. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367:1783-1791
3. Modi S, Saura C, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2020;382:610-621
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# Toxicity profiles and guidance on managing ADC-related toxicity

—— 長庚醫院 / 郭玟伶 主任 & 長庚醫院 / 彭夢婷 醫師

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. The mechanism* of ADC toxicity is mostly related to payload release and the presence of antibody target in normal tissue. Linker stability and ADC internalization also affect on toxicity. The toxicity can present as off–tumor in the normal tissue due to on–target or off–target effect. | NA | A | 4, 9 |
| 2. The spectrum of ADC toxicities vary with different ADCs. Some toxicities may potentially lead to lethal consequences, some are unique to specific ADCs. | I | A | 1–10, 17 |
| 3. Management of common ADC toxicities is similar to that for chemotherapy toxicities. Practical measures of monitoring and management can be referred to the updated recommendation (Ref. 9). Patient education, clinical vigilance, early assessment and management are of the upmost importance.<br><br>However, special attentions mentioned herein only focus on toxicities with potentially lethal consequences, such as interstitial lung disease (ILD), and particular toxicities more commonly associated with ADCs. | I | A | 1 |
| 4. Drug–induced pneumonitis/ILD occur in about 10% of patients receiving T–DXd and other ADCs to lesser degrees. The mechanism can be related to cytotoxic or immune–related damage to the lung tissue. General management principle includes:<br>· Careful evaluation of clinical symptoms, history of exposures, chest image, pulmonary function and laboratory tests are important for early diagnosis and grading of severity.<br>· Prompt start of steroid is suggested for grade 2 or above and can be considered for grade 1.<br>· Rechallenge of T–DXd after recovery is limited to grade 1 pneumonitis, while permanent discontinuation of T–DXd is necessary for pneumonitis of and above grade 2. The monitoring and management should be referred to the updated guidelines (Ref 2). | II | A | 1, 2, 6 |
| 5. Ocular toxicity of ADC range from corneal epithelial alteration, conjunctivitis to lacrimal ductal inflammation. Dry eye, blurred vision, visual impairment and increased lacrimation are common presentations. Including an ophthalmologist for regular assessment and prophylactic lubricating eye drop is encouraged. All grade ocular toxicity occurs at an incidence of 3–6% in T–DM1 and T–DXd, and at a higher rate of 16–21% in Datopotamab deruxtecan (Dato–DXd), mostly of mild severity. | I | A | 1, 13–16 |
| 6. Oral mucositis or stomatitis occur in 50–70% in patients treated with certain ADCs such as Dato–DXd, of which are mild mostly. Early dental assessment, improving oral hygiene, steroid mouth wash, ice chips, oral topical antifungal agent, and dietary attention can be applied to avoid further complications such as bleeding, malnutrition and superficial infection.† | II | A | 1, 11, 12 |

* More specific mechanisms of ADC toxicity include:1)Target–induced toxicity, 2) FcR–driven toxicity, 3) Pinocytosis–drive toxicity, 4) Bystander effect *(i.e., unintentional payload diffusion from Ag (+) tumor cells to adjacent Ag(–) tumor cells, which amplifies the effect of local tumor killing).*

† Due to high expression of TROP–2 in proximal digestive tract cell and oral mucosa

## ◎ Reference


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# Understanding the activity of antibody-drug conjugates in brain metastasis: Current indications and future perspectives

—— 成大醫院 / 鍾為邦 醫師

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. T-DXd can effectively manage systemic disease and brain metastases in patients with HER2-positive MBC. The use of T-DXd can still offer a substantial intracranial control even in patients with untreated or previously treated and progressing brain metastasis. | I | A | 1, 2 |
| 2. T-DM1 offers certain advantages for patients with HER2-positive metastatic breast cancer and stable brain metastases. It may serve as an alternative when T-DXd is unavailable. | II | B | 3 |
| 3. We need additional data to determine which patients with metastatic TNBC and stable brain metastases can benefit more from SG. | II | B | 4-6 |

* Insufficient evidence exists to assess the efficacy of T-DXd in patients with metastatic HER2-low breast cancer and brain metastases.

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# Sequential use of ADCs with and without an interruption: both target and payload matter?

—— 中國附醫 / 黃至豪 醫師

| 2024 Consensus Statement | Quality of Evidence | Strength of Recommendation | Key Reference |
|---|---|---|---|
| 1. Sequential use of an ADC after another ADC an acceptable treatment strategy. When patients receiving a second ADC, there should be at least one difference in either the target mechanism or payload. However, subsequent use of an ADC, especially with the same target or payload mechanism, tends to show poor efficacy compared to frontline use. | II | B | 1–9 |
| 2. There is still no evidence of an optimal ADC sequence, and the effects of having an interruption between two ADC treatments for patients receiving a second ADC remain undetermined. | II | B | 3, 5–8, 10–12 |

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## Note

2024

# ADC CONSENSUS SYMPOSIUM

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TAIWAN BREAST CANCER SOCIETY